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Articles

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Longterm Mortality Outcome in Patients with Rheumatoid Arthritis: Early Presenters Continue To Do Well

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ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) have reduced life expectancy; however, there are few data on the changing pattern of causes of death with longterm followup, or on the longterm effect of early presentation. The objectives of this study were (1) to examine the effect of early presentation on subsequent mortality; (2) to compare the causes of death early and late in the followup period; and (3) to compare survival of the cohort with that of the general population (adjusted for age and sex) over a followup period of up to 27 years.

Methods. A cohort of 448 patients with RA (inpatients and outpatients), assembled 1968-74, were followed to December 31, 1990. Death certificates were obtained for all who had died and coded using the International Classification of Diseases. Kaplan-Meier survival curves were constructed.

Results. By the end of the study, 266 patients (59%) had died. The standardized mortality ratio (SMR) was 2.7 (95% CI 2.4-3.1). Patients who presented early continued to do well. Most excess deaths were due to cardiovascular disease. SMR due to infection, renal failure, and non-Hodgkin's lymphoma rose with disease duration.

Conclusion. Patients with RA should be referred early, and those with chronic disease should be closely monitored for evidence of infection and renal impairment. (J Rheumatol 1998;25:1072–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OUTCOME MORTALITY CAUSE OF DEATH

In the past 50 years, 16 centers in North America and Europe have reported the mortality experiences of cohorts of patients with rheumatoid arthritis (RA) (reviewed in Grimstadt-Kvalvik, 1996[1]). All except one, a population based study[2], have shown a reduced life expectancy for patients with RA.

A few centers have reported on the same group of patients after increasing periods of followup. Two of these were incidence cohorts of patients seen within one year of RA onset. From a group of 100 patients with early RA seen in Bath, England, between 1957 and 1963, 17 had died by 11 years of followup[3], 43 by 18 years[4], and 63 by 25 years[5]. Forty-two percent of the 12 deaths attributable to RA occurred in the first 11 years, compared to only 24% of the 42 unrelated deaths. RA was thought to be contributory in the remaining 9 deaths. From a group of 102 patients with early RA seen in London, England, between 1966 and 1971, 10 had died by 5 years of followup[6] and 29 by 15 years[7]. The only death attributable to RA occurred in the first 5 years.

A group from Finland has reported on a cohort of 1000 patients with prevalent RA (50% male) aged over 40 in 1970 and followed for 3[8], 5[9], and 10 years[10]. An age, sex, and area of residence matched cohort of controls was also followed. By 10 years, 208 (41.6%) males and 148 (29.6%) females had died, compared to 144 (28.8%) and 73 (14.6%) of the controls, respectively. Sixty-four percent of the deaths due to infection occurred in the first 5 years of followup, compared to only 45% of the deaths due to renal failure.

These findings suggest that the pattern of cause of death in patients with RA may change with disease duration. Other studies have suggested that the excess mortality in RA increases progressively with disease duration[11]. However, in studies using standardized mortality ratio (SMR) (the observed number of deaths divided by the expected number of deaths in an age and sex matched sample of the general population) one would expect the point estimate of the SMR to approach 1.0 as the length of followup increases. This is because all members of the RA cohort and of the matched population sample will eventually die, and because deaths unrelated to RA will become more prominent with increasing age.

We report the mortality experience of a cohort of 489 patients with RA assembled between 1964 and 1978. The SMR and cause of death were reported after a mean

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followup of 11.4 years[12]. This study extends the mean followup of the survivors to 21.5 years.

MATERIALS AND METHODS

The cohort comprised 489 consecutive patients seen by the rheumatology staff of the Queen Elizabeth Hospital, Birmingham, England, between 1964 and 1978. All satisfied the 1958 American Rheumatism Association criteria for RA[13] and were under the care of the late Dr. Clifford Hawkins. All patients were followed via the National Health Service (NHS) Central Register. The NHS central register holds the details of all individuals in England and Wales registered with a general practitioner (the vast majority of the population). Copies of all death certificates are sent to the NHS Central Registry. The patients were originally followed to December 31, 1981[12]. Sufficient information for tracing and analysis was available at that time on 448 patients, of whom 199 (44%) had died during the followup period. The records of these 448 patients were "tagged" at the NHS Registry and the present study extends the period of followup to December 31, 1990.

The cohort are considered as 4 groups that are not mutually exclusive (Table 1, Figure 1): all the patients (n = 448); patients who presented to hospital within 5 years of onset — the early presenters (n = 252); patients who presented to hospital more than 5 years from onset (n = 196) — the late presenters; and patients who had disease onset after the start of the study (January 1, 1964) — the inception cohort (n = 162). The inception cohort is a more representative sample of "all patients with RA who are referred to hospital" since, potentially, it includes patients with all possible outcomes. In this particular study patients with onset before January 1, 1964, include the survivors of an unknown cohort of patients referred to hospital before that date, some of whom were discharged and some of whom died before January 1, 1964.

Copies of death certificates were obtained from the NHS Central Registry for all those who had died. The underlying cause of death was coded using the 8th revision of the International Classification of Diseases (ICD)[14] for deaths up to and including December 31, 1981, and the 9th revision of the ICD[15] for deaths from January 1, 1982, up to and including December 31, 1990.

Age and sex specific person-years at risk were computed from the date first seen at hospital after January 1, 1964, to December 31, 1990, or until death. Expected numbers of deaths were calculated for all causes and for 7 main-group causes by applying the appropriate mortality rates for England and Wales to the person-years at risk. Population estimates based on the 1971 census[16,17] were used to calculate the mortality rates up to December 31, 1981, and on the 1981 census[18,19] for mortality rates from January 1, 1982, to December 31, 1990. The numerator of the expected mortality rates was taken from published sources of cause of death by year for England and Wales. Thus changes in mortality rate of the general population over the period of the study were taken into account. Results are expressed as SMR with 95% confidence intervals (95% CI).

Kaplan-Meier curves were constructed for the inception cohort in order to compare the survival of the patients with RA with that of the general population for each year of followup. The 2 curves were compared using the log-rank significance test[20].

RESULTS

Mortality. The series included 155 men and 293 women. Of the original 448 patients, 199 (44%) had died by December 31, 1981[12]. By December 31, 1990, an additional 67 patients had died, making a total of 266 deaths (59%). Patients for whom no death certificate had been received by the end of December 1992 with a date of death before January 1, 1991, were assumed to be alive on December 31, 1990. In total, 103 (66%) of the men and 163 (56%) of the women died. There were 6739 person-years of followup. The mean followup of survivors was 21.5 years (range 12–27). Sixty-four (40%) of the inception cohort and 129 (51%) of the early presenters had died.

Survival curves. Details of the inception cohort are shown in Table 2. Kaplan-Meier curves for the inception cohort (Figure 2) show that both men and women with RA have a reduced life expectancy. For men this difference in mortality

Table 2. Characteristics of inception cohort of 162 patients with disease onset on or after January 1, 1964.

	Male	Female	Total
Number of patients	61	101	162
Mean followup of survivors, patient-years	16.4	19.4	18.3
Mean age at onset, yrs	45.9	42.6	43.9

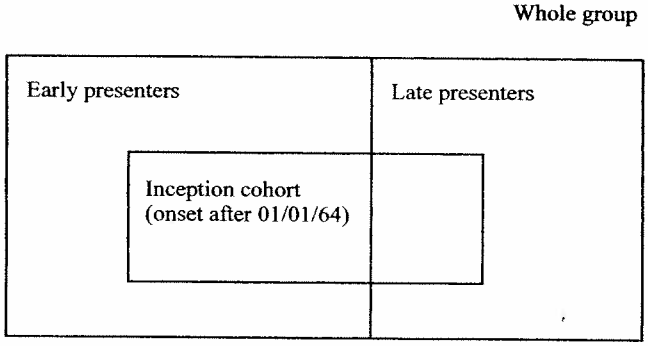

Figure 1. Subgroups included within the original cohort of 448 patients with RA: early presenters (seen within 5 years of RA onset); late presenters (first seen in hospital more than 5 years after onset); inception cohort (onset of disease after January 1, 1964).

Table 1. Patients with RA considered in this report.

	Whole Cohort	Early Presenters (≤ 5 yrs disease at presentation)	Late Presenters (> 5 yrs disease at presentation)	Inception Cohort (Onset after 1/1/64)
N	448	252	196	162
Male	155	95	60	61
Female	293	157	136	101
Numbers of deaths (%)	266 (59)	129 (51)	137 (70)	64 (40)
Mean age when first seen in hospital, yrs	47.5	45.4	50.3	48.6

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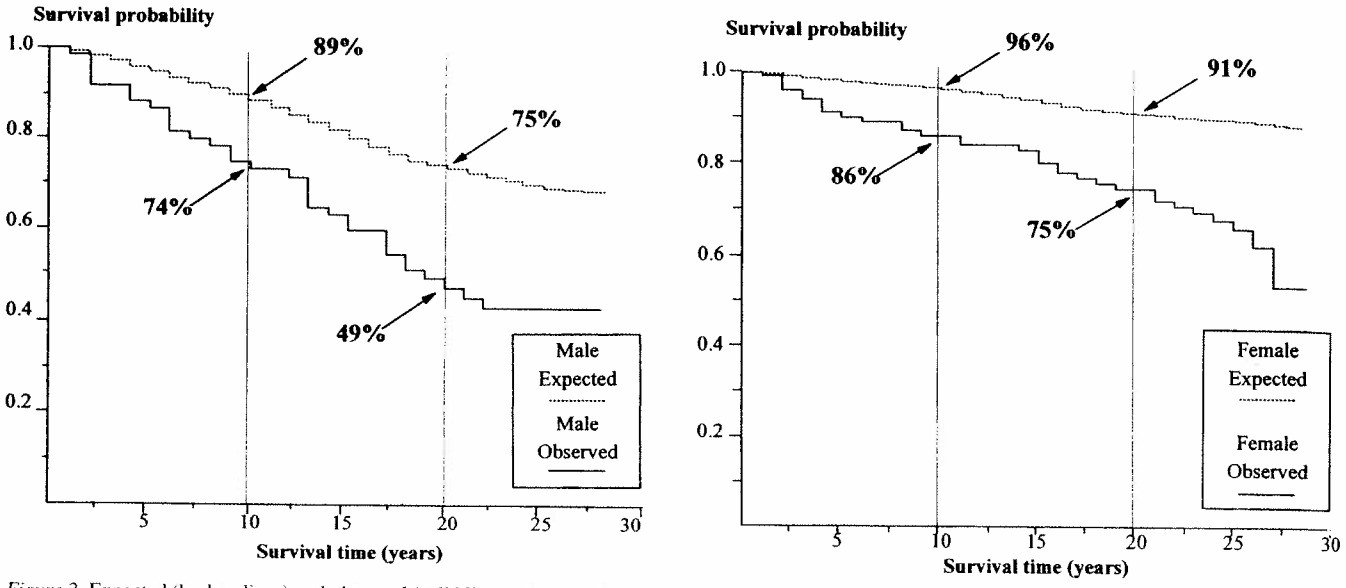

Figure 2. Expected (broken lines) and observed (solid lines) Kaplan-Meier survival curves for male (n = 61) and female (n = 101) patients with disease onset on or after January 1, 1964.

reaches statistical significance after 7 years followup and for women after 4 years followup. The difference in life expectancy continues to increase up to 20 years followup.

Cause of death. There were no major changes in the grouping of causes of death (ICD chapter headings) between ICD8 and ICD9. It is thus possible to combine and compare the SMR for the main groupings for the periods January 1, 1964–December 31, 1981; January 1, 1982–December 31, 1990; and January 1, 1964–December 31, 1990 (Table 3). As expected, the all-cause SMR falls as the period of followup is extended, although the relative risk of death remains significantly elevated at 2.7 (95% CI 2.4–3.1). This phenomenon is also seen for all the main-group causes except infection and the genitourinary system. There is a marginal increase in the SMR for malignancy. Table 4 shows the change in the proportion of deaths due to main-group causes in the 2 followup periods.

Most deaths from infection were due to septicemia (pneumonia and bronchopneumonia are coded under respiratory causes). Three patients died from septic arthritis. All the genitourinary deaths were due to renal failure. In total, renal failure was noted on 16 death certificates (in 6 it was not the main cause of death). In 5 cases no underlying reason for the renal failure was given. In the remaining 11, renal failure was attributed to renal calculi in 4, amyloidosis in 2, and pyelonephritis, septicemia, tuberculosis, systemic lupus erythematosus, and obstructive jaundice in one case each. Most deaths directly attributed to RA (33/40, 82.5%) occurred in the first period of followup.

We have reported an increase in cancer morbidity and mortality in this cohort[21], with all the excess malignancies being neoplasms of the immune system (NIM) (leukemia, lymphoma, or myeloma). An additional 4 deaths from NIM (3 from non-Hodgkin's lymphoma, one from Hodgkin's disease) occurred between 1982 and 1990 (Table 5). This was significantly more than expected in this period (SMR = 8.9; 95% CI 2.4–22.9). The SMR for non-Hodgkin's lymphoma rose to 81.1 (95% CI 16.7–237.0) in the second followup period. However, the change was not statistically significant (ratio of SMR 3.1, 95% CI 0.5–15.8). There were no new deaths from leukemia. It therefore appears likely that the relative risk of dying from NIM, and in particular non-Hodgkin's lymphoma, rises with increasing disease duration, although the study population was too small for the changes with time to be statistically significant.

Mortality and early presenters. We reported lower SMR in the patients who presented to hospital within 5 years of RA onset[22] (Group 1 in Table 6). It was impossible to tell whether this was because the excess mortality in RA rises with disease duration, whether early treatment of RA reduces mortality, or whether early presenters have milder disease. To examine these possibilities further we compared the mortality experience of the late presenters (Group 2 in Table 6) during the first period of followup with that of early presenters (Group 1) in the second period of followup. The mean disease duration of the 196 late presenters at the time first seen in hospital was 12.6 years (range 5.0–40.8). The mean disease duration of the surviving 153 early presenters on January 1, 1982, was 15.7 years (range 4.8–22.6). The SMR of the early presenters continue to be lower than those of the late presenters. As with the whole cohort, the early presenters show a rise in the SMR due to infection and renal disease, and a fall in SMR for deaths directly attributed to RA.

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Table 3. Rheumatoid arthritis: mortality by cause for 7 specific categories of ICD (8th and 9th revisions), whole cohort of patients.

Cause of Death (based on ICD chapter)	Period from Date First Seen After 1/1/64–31/12/81 Observed Deaths	SMR (95% CI)	Period 1/1/82–31/12/90 Observed Deaths	SMR (95% CI)	Period from Date First Seen After 1/1/64–31/12/90 Observed Deaths	SMR (95% CI)
All causes						
Male	82	2.6 (2.0–3.2)	21	1.9 (1.1–2.8)	103	2.4 (1.9–2.9)
Female	117	3.4 (2.8–4.0)	46	2.3 (1.7–3.1)	163	3.0 (2.6–3.5)
Total	199	3.0 (2.6–3.4)	67	2.1 (1.6–2.6)	266	2.7 (2.3–3.1)
Infections						
Male	1	5.3 (0.0–21.1)	0	—	1	4.4 (0.0–17.4)
Female	3	17.6 (3.2–43.9)	3	43.5 (9.0–127.0)	6	25.0 (8.8–50.0)
Total	4	11.1 (2.8–25.0)	3	36.6 (10.0–93.6)	7	14.9 (5.8–28.3)
Malignant neoplasms						
Male	12	1.5 (0.8–2.5)	6	1.9 (0.7–4.0)	18	1.6 (0.9–2.5)
Female	18	1.8 (1.0–2.7)	9	1.5 (0.7–2.9)	27	1.7 (1.1–2.5)
Total	30	1.6 (1.1–2.3)	15	1.9 (1.1–3.2)	45	1.7 (1.2–2.2)
Circulatory system						
Male	39	2.4 (1.7–3.2)	7	1.2 (0.5–2.6)	46	2.1 (1.5–2.8)
Female	39	2.3 (1.7–3.2)	19	2.0 (1.2–3.2)	58	2.2 (1.7–2.8)
Total	78	2.4 (1.9–2.9)	26	1.8 (1.2–2.6)	104	2.2 (1.8–2.6)
Respiratory system						
Male	10	2.4 (1.1–4.1)	2	1.3 (0.2–4.7)	12	2.1 (1.1–3.5)
Female	19	6.1 (3.6–9.2)	8	3.7 (1.6–7.2)	27	5.1 (3.3–7.3)
Total	29	3.9 (2.6–5.5)	10	2.9 (1.4–5.4)	39	3.6 (2.5–4.8)
Digestive system						
Male	6	8.3 (2.9–16.5)	0	—	6	6.1 (2.1–12.0)
Female	5	5.1 (1.6–10.7)	2	3.1 (0.3–11.2)	7	4.3 (1.7–8.1)
Total	11	6.5 (3.2–11.0)	2	2.2 (0.3–8.0)	13	5.0 (2.6–8.1)
Genitourinary system						
Male	1	2.6 (0.0–10.3)	3	22.3 (4.6–65.5)	4	7.7 (1.9–17.3)
Female	5	10.0 (3.1–20.9)	1	3.9 (0.1–21.5)	6	7.9 (2.8–15.7)
Total	6	6.7 (2.4–13.4)	4	10.3 (2.8–26.5)	10	7.8 (3.7–13.5)
Musculoskeletal system						
Male	12	150.0 (75.9–249.1)	2	66.9 (8.1–242.0)	14	127.3 (68.3–204.4)
Female	22	88.0 (54.5–120.5)	4	28.5 (7.8–73.0)	26	66.6 (43.1–95.4)
Total	33	103.0 (70.7–141.4)	6	39.0 (15.7–80.3)	40	80.0 (56.7–107.3)
Remainder						
Male	1	0.5 (0.0–2.2)	1	2.0 (0.1–11.1)	2	0.8 (0.1–2.4)
Female	6	2.0 (0.7–4.0)	0	—	6	1.4 (0.5–2.8)
Total	7	1.5 (0.6–2.8)	1	0.5 (0.0–2.8)	8	1.2 (0.5–2.2)

Table 4. Proportion of deaths due to different main-group causes in the 2 followup periods.

	Period 1 (1/1/64–31/12/81), % of Deaths	Period 2 (1/1/82–31/12/90), % of Deaths	Total (1/1/64–31/12/90), % of Deaths
Infection	2.0	4.5	2.6
Malignancy	15.1	22.4	16.9
Circulatory system	39.2	38.8	39.1
Respiratory system	14.6	14.9	14.7
Digestive system	5.5	3.0	4.9
Genitourinary system	3.0	6.0	3.8
Musculoskeletal	16.6	10.4	15.0
Remainder	3.5	1.5	3.0
Total number of deaths	199	67	266

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Table 5. Mortality from malignant neoplasms in 448 patients with RA.

Cause (ICD)	Period from Date First Seen After 1/1/64–31/12/81		Period from 1/1/82–31/12/90		Period from Date First Seen After 1/1/64–31/12/90	
	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)
Malignant neoplasms	30	1.6 (1.1–2.3)	15	1.9 (1.1–3.2)	45	1.7 (1.2–2.2)
Non-Hodgkin's lymphoma	5	26.3 (8.0–55.1)	3	81.1 (16.7–23.7)	8	35.1 (14.7–64.4)
Hodgkin's lymphoma	0	—	1	5.2 (0.1–28.9)	1	1.7 (0.0–2.4)
Leukemia	3	7.9 (1.4–19.6)	0	—	3	5.3 (0.9–13.3)
Remainder	22	1.2 (0.8–1.8)	11	1.6 (0.8–2.8)	33	1.3 (0.9–1.8)
NIM	8	8.3 (3.5–15.1)	4	8.9 (2.4–22.9)	12	8.5 (4.3–14.0)

NIM: neoplasms of the immune system (lymphomas, leukemias, and myelomas).

Table 6. Mortality by cause for 252 early presenters with RA (Group 1), who had < 5 years' disease duration when first seen, and for 196 late presenters (Group 2), who had > 5 years' disease duration when first seen.

Cause (ICD)	Group 1 From Date First Seen After 1/1/64–31/12/81		Group 1 From 01/01/82–31/12/90		Group 2 From Date First Seen After 1/1/64–31/12/81	
	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)
All causes	91	2.5 (2.0–3.0)	38	1.8 (1.3–2.5)	108	3.6 (2.9–4.3)
Infections	1	4.8 (0.0–19.0)	3	42.5 (7.6–105.7)	3	20.0 (3.6–49.8)
Malignant neoplasms	19	1.9 (1.1–2.8)	7	1.3 (0.5–2.4)	11	1.4 (0.7–2.3)
Circulatory system	35	2.0 (1.4–2.7)	16	1.6 (0.9–2.4)	43	2.8 (2.0–3.8)
Respiratory system	14	3.5 (1.9–5.6)	4	1.6 (0.4–3.6)	15	4.5 (2.5–7.2)
Digestive system	4	4.4 (1.1–9.9)	2	3.2 (0.3–9.4)	7	8.9 (3.4–16.8)
Genitourinary system	0	—	2	7.5 (0.6–21.8)	6	14.6 (5.1–29.0)
Musculoskeletal system	14	82.4 (44.2–132.3)	4	34.8 (8.7–78.4)	20	125.0 (75.3–187.1)
Remainder	4	1.5 (0.4–3.4)	0	—	3	1.4 (0.2–3.5)

DISCUSSION

This is the second report concerning a cohort of 448 patients with RA assembled in Birmingham, UK, in 1964–1978. Fifty-nine percent have died. The survivors have been followed for a mean of 21.5 years. The findings show clearly that the pattern of death, measured using SMR, changes with disease duration and the length of followup. Deaths from infection, renal failure, and non-Hodgkin's lymphoma increase progressively with disease duration, while deaths attributed to RA tend to occur early in disease. Only the change in deaths attributed to RA was statistically significant, because the number of observed deaths in the second period in these categories was small. In the older literature, investigators often decided whether deaths were "attributable" to RA, "related," or "unrelated." Clearly, such judgments may be subject to attribution bias. In this study, deaths attributed to RA are those for which RA was given as the underlying cause of death on the death certificate. In the great majority of cases, the death certificate was not completed by the rheumatologist but by the attending physician, usually the GP.

In 1994, Wolfe, *et al*[11] reported the mortality experience of 3501 patients from 4 centers (one community based, one office based, one a secondary referral center, one a tertiary referral center). The survival curves from the present study most closely match those from Saskatoon, with male survival of 74% at 10 years and 49% at 20 years and female survival of 86 and 75%, respectively. Both Saskatoon and Queen Elizabeth Hospital, Birmingham, are university hospitals and the only referral center for a large catchment population. Both cohorts were assembled over a similar time period. All 4 survival curves from the Wolfe study and that of the present study emphasize that the difference between mortality experience of patients with RA and the general population increases with disease duration. This fact is lost in studies that present only summary SMR, since the SMR takes no account of when during the followup period the deaths occurred.

Early presenters continued to do better than late presenters even after 15 years' disease duration. This suggests that the high mortality found among late presenters in our original report[22] was not simply because mortality increases with disease duration, but must also be either because those who present early have milder disease or because early treatment improves prognosis, or both.

In ICD most infections are included under the organ

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system in which they occur. Increased risk of death from pneumonia and bronchopneumonia may therefore be masked in this study. Of the 39 respiratory system deaths, 31 (79%) were due to respiratory infections. Many studies have found an increase in deaths from infection in RA[4,10,11,23], but it has not previously been confirmed that this risk increases with disease duration. As in this study, the Finnish group reported an increasing risk of death from renal failure with increasing length of followup[10]. However, 43% of the RA deaths due to renal failure in Finland were attributed to amyloidosis compared to only 20% in the present series.

One area deserving greater attention is the link between RA and circulatory deaths. As in other series[11], this study has shown that the greatest number of excess deaths are due to circulatory disease (57 excess deaths, 34% of excess deaths). This proportion of excess deaths appears to be unaffected by time since presentation. Circulatory deaths accounted for 31% of excess deaths in the early presenters in the first period of followup and 36% in the second period of followup. They accounted for 35% of excess deaths in the late presenters. Thus the proportion of excess deaths is fairly stable and would therefore seem to be directly related to having RA rather than to a cumulative effect of the disease or its treatment. In other words, RA may be viewed as a risk factor for developing cardiovascular disease.

In summary, there is much still to be learned about the relationship between RA and premature death. Our findings suggest that early presenters continue to do well, and support the argument for early hospital referral of patients with RA. The data also show a continued high risk of death from circulatory disease, infection, and renal failure in patients with chronic RA, emphasizing the need for continued vigilance.

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